Original article
A correlative study of biochemical parameters in polycystic ovarian syndrome
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**ABSTRACT**

Background: Polycystic Ovarian Syndrome was originally described by Stein and Leventhal in 1935, as a triad consisting of amenorrhea, hirsutism and obesity, in women who had multiple cysts on their ovaries. PCOS also known as functional ovarian hyperandrogenism is a complex disorder that begins during puberty and affects reproductive-age women. It is characterized by a varied and often complex array of metabolic and endocrine abnormalities. Aim: To analyse and correlate the biochemical parameters (Glucose, Magnesium, Uric Acid and lipid profile) in women with Polycystic Ovarian Syndrome. Materials and Methods: After Ethical Committee Approval, blood samples were collected from 30 premenopausal women diagnosed to have PCOS by Rotterdam Criteria and 30 healthy controls (premenopausal women); aged 18 to 40 years. Fasting plasma glucose, serum magnesium, uric acid and lipid profile were investigated in both PCOS patients and controls. The correlation between these biochemical parameters were then studied in the PCOS group. Result: There was a significant increase in fasting plasma glucose (P < 0.001) and serum uric acid (P< 0.0001) levels with decrease in serum magnesium (P < 0.01) levels in PCOS patients as compared to controls. PCOS women had higher BMI (P < 0.0001) with increased total cholesterol (P < 0.0001), TGL (P < 0.0001), LDL-C (P < 0.0001), VLDL-C (P < 0.0001) and lower HDL-C (P < 0.0001) as compared to the controls which was statistically significant. The levels of glucose showed significant positive correlation with uric acid (r = 0.53; P = 0.002), total cholesterol(r = 0.48; P = 0.006), triglycerides(r = 0.52; P = 0.002), LDL-C(r = 0.44; P < 0.01) and highly significant negative correlation with magnesium (r = -0.85; P < 0.0001) whereas non-significant negative correlation with HDL-C. Uric Acid showed significant negative correlation with HDL-C (r = -0.39; P = 0.02). No correlation was found between uric acid and magnesium, total cholesterol, triglycerides, LDL-C and VLDL-C. Conclusion: The findings of this study confirms the association between Glucose, Magnesium, Uric Acid, BMI and dyslipidaemia in PCOS and may help to identify women with PCOS at risk of cardio metabolic syndrome thereby confirming the association between PCOS and cardiovascular risk factors.

1. Introduction

Polycystic Ovarian Syndrome (PCOS) is the most common female endocrine disorder with a prevalence of ~5-10% in women of reproductive age [1]. PCOS is characterized by increased ovarian and adrenal androgen secretion, hyperandrogenic metabolic.

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...syndrome symptoms such as hirsutism, acne and/or alopecia, menstrual irregularity and polycystic ovaries. PCOS is not only a reproductive endocrinopathy but also a metabolic disorder [2]. One of the most prominent metabolic symptoms of PCOS is insulin resistance which includes two conditions-Hyperinsulinemia and Impaired Glucose Tolerance.

Women with PCOS are known to be at increased risk for insulin resistance [3]. In Insulin Resistance, the body becomes increasingly less responsive to the action of insulin. As a result, there is more circulating glucose in the blood waiting to be absorbed into the cells resulting in impaired glucose tolerance.
Women with PCOS also develop abnormal glucose metabolism at a younger age and may demonstrate a more rapid conversion from impaired glucose tolerance to type II diabetes mellitus [4].

Magnesium, a cofactor of many enzymes involved in glucose metabolism, is required for both proper glucose utilization and insulin signalling. In particular it has been shown that magnesium plays the role of a second messenger for insulin action [5]. Low magnesium concentrations are associated with impaired glucose tolerance and increased risk for type II diabetes mellitus. It is currently unknown whether women with PCOS exhibit serum magnesium deficiency and its potential association with glycemic levels.

Uric Acid is a metabolic end product of purine metabolism. It is a strong reducing agent and potent antioxidant. The possible relationship between androgens and serum uric acid concentrations is supported by animal experiments showing that androgens may increase serum uric acid levels by inducing the hepatic metabolism of purines [6]. The studies available at present regarding serum uric acid levels in PCOS patients are scarce and led to controversial results. Obesity and excess weight are major chronic diseases in western world countries. Obesity increases hyperandrogenism, hirsutism, infertility and pregnancy complications both independently and by exacerbating PCOS. Likewise, in PCOS obesity worsens insulin resistance and exacerbates reproductive and metabolic features [7].

Adiposity plays a crucial role in the development and maintenance of PCOS and strongly influences the severity of both its clinical and endocrine features in many women with the condition. In addition to its effects on insulin sensitivity, the adipocyte is also involved in the metabolism and interconversion of various steroid hormones in both normal women and men. The mechanism relating adiposity to PCOS relates to the consequences of increasing body mass on steroid metabolism. It has been proposed that PCOS may result from reduced aromatase activity [8].

There is some evidence that women with PCOS have enhanced peripheral 5α-reductase activity compared with age and BMI matched control women thereby generating higher tissue concentrations of more potent androgen DHT [8]. Increased 5α-reductase activity in the adipocyte could therefore be one mechanism by which obese women with PCOS display increased androgenicity. In addition to abnormal distribution of adipose tissue in women with PCOS, there may also be inherent abnormalities of lipolysis within adipocytes that are site specific [8]. Women with PCOS have disturbed lipid profiles. The causes of dyslipidaemia in PCOS are again multifactorial. Insulin Resistance appears to have a pivotal role; mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase [9]. PCOS is a chronic disease with manifestations across the lifespan and represents a major health and economic burden. Diagnosis of PCOS is extremely important because it in turn identifies risk for potential metabolic and cardiovascular diseases. Several biochemical and clinical features of PCOS resemble those of metabolic syndrome: women with PCOS are often obese and at increased risk of developing diabetes mellitus and cardiovascular diseases. Therefore, it is recommended that women with PCOS be routinely screened so that treatment can be initiated earlier. The increased incidence of cardiovascular disease in women with PCOS has prompted researches to look for indicators of early metabolic changes in these patients. In view of this, the present study was undertaken to analyse and correlate the biochemical parameters that may help to identify women with PCOS at risk of Cardio Metabolic syndrome.

2. MATERIALS AND METHODS

Study Population:

The Observational Epidemiological Case Control Study was carried out in the department of Obstetrics and Gynaecology at Shri Sathya Sai Medical College and Research Institute from August to September, 2012. A total of 60 consented women aged 18-40 years were enrolled in the study. These subjects were divided into two groups (patients and controls). The study group consisted of 30 premenopausal women diagnosed to have Polycystic Ovarian Syndrome (PCOS) by Rotterdam criteria. The control group consisted of 30 age matched healthy female volunteers with regular menstrual cycles and with no clinical or biochemical features of hyperandrogenism, thereby excluding the diagnosis of PCOS in this group. Institutional Ethical Committee approval was obtained. The participation of the respondents was voluntary and informed consent was signed by each participant.

All subjects answered a questionnaire which contained details of age, menstrual history, medical history and family history of type 2 diabetes mellitus or polycystic ovarian syndrome.

Inclusion Criteria:

I. Diagnosis based on Rotterdam Criteria (2003):
   1. Oligomenorrhoea/Amenorrhea
   2. Clinical / Biochemical signs of Hyperandrogenism
      a. Hirsutism
      b. Acne
      c. Alopecia
   d. Elevated androgen levels (Testosterone)
   3. Presence of Polycystic ovaries on ultrasound scans

II. LH/FSH Ratio

Exclusion Criteria:

- Diabetes Mellitus
- Hypertension
- Thyroid Disorders
- Renal Diseases
- Cardiovascular Diseases
- Cushing’s Syndrome
- Pregnant or lactating women
- Oral Contraceptives
- Hypoglycemic agents / Lipid lowering drugs
- Hormonal Medications within previous 6 weeks
Anthropometric Measurement

**Body Mass Index:**

All the subjects’ height and weight were recorded without shoes using standard apparatus.

Body mass index (BMI) was calculated by dividing weight (kg) by height (m$^2$). Normal weight was defined as BMI < 25, Overweight as BMI between 25.0-29.9 and Obesity as BMI > 30.

**Blood Pressure:**

Blood pressure was measured in the right arm, with the subjects in a relaxed sitting position using a mercury sphygmomanometer.

**Sample Collection and Storage:**

5 ml of venous blood samples was collected from healthy controls and women with PCOS after an overnight fast. 1 ml of sample was taken in a tube containing anticoagulant and analysed for plasma glucose. 4 ml of sample was taken in a plain tube. After centrifugation at 3000 rpm for 10 minutes, the serum samples were incubated for 15 minutes at room temperature and analysed for Magnesium, Uric Acid and Lipid Profile using standard kits (ERBA: Glucose, Uric Acid, Total-Cholesterol, Triglycerides, High Density Lipoprotein-Cholesterol [HDL-C] and AVECON: Magnesium) in Semi-Auto analyser (Biosystems BTS 350) either on the same day of collection or stored at 2-8°C until further analysis.

**Biochemical Methods**

I. Plasma glucose was analysed by Glucose Oxidase-Peroxidase Method

II. Serum sample was used for following biochemical assays:

a) Magnesium was estimated by Xylyl Blue Method

b) Uric Acid was estimated by Modified Trinder Method

c) Lipid Profile:
- Total Cholesterol (Cholesterol Oxidase Method)
- Triglycerides (Glycerol Phosphate Oxidase and Peroxidase Method)
- High Density Lipoprotein Cholesterol (Phosphotungstic Acid Method)
- LDL-C and VLDL-C were calculated using the Friedewald’s formula:

\[
\text{LDL Cholesterol} = \frac{\text{Total cholesterol} - \text{HDL Cholesterol} - \text{Triglyceride}}{5}
\]

\[
\text{VLDL Cholesterol} = \frac{\text{Triglyceride}}{5}
\]

(Where all concentrations are given in mgs/dl)

**Statistical Analysis:**

Data Analysis was performed using SPSS 20 Software. The values were expressed as mean ± Standard deviation. Pearson’s correlation coefficients were calculated to assess the correlation between the biochemical parameters in the study group. A P value of < 0.05 was considered statistically significant. 'P' value with single star (*) represents significance and 'P' value with 2 or 3 stars (***') represents higher significance.

3. RESULTS

Table I shows the mean, standard deviation and P values of anthropometric measurements in PCOS patients and controls. The mean age of the PCOS group and the control group were 26.2 and 28.16 respectively (P = 0.05). PCOS patients had significantly higher BMI (P < 0.0001***), Systolic Blood Pressure (P < 0.0001***), and Diastolic blood pressure (P < 0.01*) as compared to controls.

Table I. Mean, Standard Deviation and P Values of Anthropometric Measurements in PCOS Patients and Control Groups.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CONTROLS (N=30)</th>
<th>PATIENTS (N=30)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>28.16 ± 3.85</td>
<td>26.2 ± 3.83</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 1.66</td>
<td>28.03 ± 2.22</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>108.06 ± 4.43</td>
<td>116.7 ± 5.65</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>76 ± 5.82</td>
<td>79 ± 4.29</td>
<td>&lt; 0.01*</td>
</tr>
</tbody>
</table>

A P value<0.05 was considered statistically significant.

Table II shows the mean, standard deviation and P values of all the biochemical parameters in PCOS patients and controls. The PCOS group showed a significantly higher fasting glucose (P < 0.001**), and significantly lower serum magnesium (P < 0.01*) levels than the control group. Serum uric acid was also significantly higher in PCOS patients as compared to controls (P < 0.0001***). PCOS patients had increased total cholesterol, triglycerides, LDL-C, VLDL-C and decreased HDL-C as compared to the controls which were statistically significant (P < 0.0001***).

Table II. Mean, Standard Deviation and P Values of Biochemical Parameters in PCOS Patients and Control Groups.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CONTROLS (N=30)</th>
<th>PATIENTS (N=30)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>99.3 ± 9.32</td>
<td>98.3 ± 9.32</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2.66 ± 0.43</td>
<td>2.41 ± 0.30</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>Uric Acid (mg/dl)</td>
<td>3.92 ± 0.43</td>
<td>4.72 ± 0.53</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>166.66 ± 10.98</td>
<td>182.13 ± 9.26</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>TGL (mg/dl)</td>
<td>94 ± 12</td>
<td>116.78 ± 12.90</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>51.46 ± 5.58</td>
<td>40.35 ± 5.90</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>96.4 ± 9.55</td>
<td>118.51 ± 9.07</td>
<td>&lt; 0.0001***</td>
</tr>
<tr>
<td>VLDL-C (mg/dl)</td>
<td>18.1 ± 2.40</td>
<td>23.35 ± 2.58</td>
<td>&lt; 0.0001***</td>
</tr>
</tbody>
</table>

A P value<0.05 was considered statistically significant.
Table III summarizes the correlation coefficients and P values of BMI with biochemical parameters in the study group (PCOS group). BMI showed a significantly positive correlation with glucose (r = 0.83; P < 0.0001), uric acid (r = 0.48; P = 0.006), total cholesterol (r = 0.71; P < 0.0001), triglycerides (r = 0.73, P < 0.0001), LDL-C (r = 0.62; P = 0.002), and VLDL-C (r = 0.73; P < 0.0001), and nonsignificant negative correlation with HDL-C (r = -0.25; P = 0.18).

A P value < 0.05 was considered statistically significant.

Table IV summarizes the correlation coefficients and P values of biochemical parameters in the study group (PCOS group). The correlation between glucose and magnesium in PCOS patients was highly negatively significant (r = -0.85, P < 0.0001). Glucose showed a significantly positive correlation with uric acid (r = 0.53, P = 0.002), total cholesterol (r = 0.48; P = 0.006), triglycerides (r = 0.52; P = 0.002), LDL-C (r = 0.44; P < 0.01), and VLDL-C (r = 0.52; P < 0.05), and non-significant negative correlation with HDL-C (r = -0.22; P > 0.23).

A P value < 0.05 was considered statistically significant.
A total number of 30 patients with confirmed diagnosis of PCOS and 30 healthy controls were selected to study the levels of anthropometric measurements and biochemical parameters (fasting Glucose, Magnesium, Uric Acid, Total cholesterol, Triglycerides, HDL-C, LDL-C and VLDL-C) and find the correlation between these biochemical parameters in PCOS patients.

PCOS women had significantly higher BMI, Systolic Blood Pressure and Diastolic Blood Pressure than the control group V.M. Vinodhini et al., (2012) showed no statistically significant differences in the mean concentrations of fasting plasma glucose between PCOS patients and healthy controls [10] whereas, a study by Azevedo MF et al., (2011) reported higher fasting glucose levels in PCOS women which was statistically significant [11]. Our result was consistent with the study of Azevedo MF et al., (2011).


According to the study of Kauffman RP et al., (2011) magnesium levels did not correspond with age, BMI, waist circumference, glycemic levels, blood pressure or lipid levels in reproductive-age women with PCOS [13]. But, the present study showed decreased magnesium levels in PCOS patients as compared to controls and a highly significant negative correlation between glucose and magnesium levels which were statistically significant.
Therefore, Intracellular magnesium deficiency may affect the development of insulin resistance and alter the glucose entry into the cell.

According to L.Anttila et al., (1996)[14] and Manuel Luque-Ramirez et al., (2008)[6] no statistically significant differences were found in the mean concentrations of uric acid between PCOS and control women. Surprisingly, in our study, we found elevated serum uric acid levels in PCOS patients as compared to the controls which were statistically significant. According to L.Anttila et al., (1996). Serum uric acid concentrations were positively correlated with BMI in the PCOS group. No correlation was found between the serum levels of uric acid and triglycerides[14]. Similar result was observed in our study. In addition, we observed a significant positive correlation between glucose and uric acid.

The present study did not rule out any significant correlation between uric acid and magnesium, total cholesterol, LDL-C and VLDL-C whereas significant negative correlation was observed between uric acid and HDL-C.

Anuradha Kalra et al., (2006) found no correlation between BMI with various lipid parameters[2]. But in our investigation, we found a significant positive correlation between BMI and total cholesterol, triglycerides, LDL-C, VLDL-C and non-significant negative correlation between BMI and HDL-C. Lipid profile was also estimated in PCOS patients and compared with the control groups. A study by Olivier Valkenburg et al., (2008) on serum lipid profile of PCOS patients showed higher levels of total cholesterol, triglycerides and LDL-C compared with controls. On the contrary, serum levels of HDL-C were significantly lower in women with PCOS[15]. Our result was also consistent with the above study. We also found a significant positive correlation between glucose and total cholesterol, triglycerides, LDL-C and non-significant negative correlation between glucose and HDL-C.

CONCLUSION

The present study showed increased fasting glucose levels and decreased magnesium levels in PCOS patients as compared to controls which were statistically significant. To the best of our knowledge, we are the first to describe an inverse association between magnesium levels and glucose levels in PCOS women. The results of this study also provided the first evidence showing significantly higher serum uric acid concentrations in PCOS patients as compared to controls and showed a positive correlation between uric acid and blood glucose levels thereby establishing the association between glucose, magnesium and uric acid.

PCOS women had higher BMI, significantly increased total cholesterol, triglycerides, LDL-C and VLDL-C. On the other hand, serum levels of HDL-C were significantly lower in this group compared to controls. The findings of this study confirm the association between BMI and dyslipidaemia in PCOS.

In addition, we observed a significant positive correlation between glucose and total cholesterol, triglycerides, LDL-C, VLDL-Calong with a positive correlation between uric acid and HDL-C.

The above results suggest the association between glucose, uric acid and dyslipidaemia. In conclusion, the use of these simple and cost-effective biochemical parameters might prove to be biomarkers in early detection of these metabolic changes and may help to identify women with PCOS at risk of cardiac metabolic syndrome, confirming the association between PCOS and cardiovascular risk factors.

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